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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,444	12/20/2005	Yuso Tomohira	Q92094	6406

23373 7590 03/02/2011

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EXAMINER	
SUTTON, DARRYL C	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/02/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/561,444	TOMOHIRA, YUSO	
	Examiner	Art Unit	
	DARRYL C. SUTTON	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *1-20,31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-30 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/2010, 11/22/2010 & 12/20/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

This Office Action is in response to the amendment filed 09/21/2010. New claim 33 has been added.

Applicant's arguments filed 09/21/2010 have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 21-24, 28-30 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akiyama et al. (US 5,593690) in view of British Plastics and Rubber (2001) as evidenced by Lochtec ApS.

Akiyama et al. teach a matrix preparation produce by dispersing a pharmaceutically active ingredient into a matrix which is solid at ambient temperature

and comprised of a fatty acid ester of a polyglycerol. The preparation has stable release-controlling ability, can be processed to fine granules, tablets or capsules and contributes to reduce the administration times of the active ingredient and side effects of the ingredient (Abstract). The present inventors have found that when an active ingredient is dispersed into a matrix being solid at ambient temperature and consisting of a fatty acid ester of a polyglycerol, which has not been employed in conventional matrix preparations, an ideal controlled release matrix preparation, particularly fine granules, can be unexpectedly prepared; and that the method uses no harmful solvents and can be easily adjusted in dissolution rate (column 1, lines 34-47, column 7, lines 36-41). The matrix material, i.e. fatty acid ester of a polyglycerol, of the instant claims is taught (column 2, lines 35 - column 3, line 7). The matrixes containing fatty acid esters of polyglycerols can be incorporated with lipids, such as glycerides, i.e. glycerol fatty acid esters, in amounts that correspond to 0.01 to 100 times the weight of the active ingredient to assist in regulating the dissolution rate of drugs (column 3, line 53 - column 4, line 18). The matrixes suitably incorporate additives being generally employed in the production of fine granules, including as binding agents such as starch, sucrose, gelatin, powdered gum, sodium carboxymethylcellulose and polyvinylpyrrolidone (column 4, lines 9-18). Active ingredients include theophylline in amounts of 0.005 to 75% of the granule (column 5, lines 26-31 and lines 55-59). The method of instant claim 23 is taught (column 6, lines 8-20 and lines 38-41). Fine granules can be coated with a coating agent, such as ethylcellulose, waxes and talc or in combinations, by a per se known method (column 6, lines 49-65). The coating of fine granules is preferably

carried out at a temperature of 25° to 70°C (column 7, lines 3-4). The granules and fine granules possess extremely stable controlled release ability being free from variation and hardly show any change in drug release after storage for a prolonged period of time. The present preparations do not produce any static charge (column 7, line 42).

Akiyama et al. do not teach fusion-coating, the hydroxyl value of the matrix materials, the triglycerol behenic acid half ester or an agitation method.

British Plastics and Rubber teach a mixer, i.e. Cyclomix 5, which is suitable for powders and provides fast intensive mixing, i.e. agitation, with good control over consistency and temperature (page 1). As evidenced by Lochtec ApS, the Cyclomix 5 mixer offers exceptional heating and cooling capabilities and is applicable in coating and granulation of powders, see page 5.

British Plastics and Rubber do not teach a sustained release medicament particle.

At the time of the invention, it would have been obvious to use a triglycerol diester of behenic acid, i.e. polyglycerol fatty acid half ester, since the fatty acid esters of polyglycerols disclosed by Akiyama et al. include a triglycerol diester of behenic acid, i.e. a polyester compound such as a diester comprised of a triglycerol of a fatty acid, i.e. behenic acid, to create the ester linkages.

Since the granules of Akiyama et al. are comprised of substantially the same components as the instant invention, the base material, i.e. the triglycerol diester of behenic acid, would reasonably be expected to possess the same hydroxyl value.

At the time of the invention, it would have been obvious to use the Cyclomix 5 of British Plastics and Rubber to produce the particles of Akiyama et al. since it would be able to perform both the granulation and coating steps, thereby eliminating the need and cost for two pieces of manufacturing equipment and since Akiyama et al. teaches that the coating can be done by any per se known method. The intensive mixing action provided by the Cyclomix 5 would reasonably be interpreted as an agitation method during the coating step.

In regard to claim 23, the prior art does not teach the specific temperature of the particulate coating. The prior art does not disclose the exact claimed values, but does overlap: in such instances even a slight overlap in range establishes a *prima facie* case of obviousness. In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003). Akiyama et al. teach that the coating is done at a temperature from 25° to 70°C, and the fatty acid ester of a polyglycerol matrix base material melts at a temperature from 40° to 150°C, versus fusion coating performed at a temperature in the vicinity of the melting point of the matrix base material of the instant claim.

Applicant argues that Akiyama et al. do not teach a fusion coating method. The fusion coating of the present invention comprises heating core particles so that a matrix base material becomes molten on the surface and fine powder present in the vicinity of the molten surface adheres thereto. Akiyama et al. do not teach an agitation method.

The Examiner disagrees.

Although the Examiner agrees that Akiyama et al. does not disclose the specific fusion coating method of the instant claims, as discussed *supra* Akiyama et al. does disclose coating core particles at temperatures 25° to 70°C, which overlap the claimed coating temperatures and by any per se known method. Depending on the core material and its melting or softening point, the temperatures disclosed by Akiyama et al. would produce a molten surface and the coating powder would be expected to adhere to the molten surface. Further, since the rejection is a 103 obviousness rejection, Akiyama et al. is not required to teach each and every limitation of the claims.

Applicant argues that Akiyama et al. does not teach a matrix base material having a hydroxyl value of 60 or greater and containing a polyglycerol fatty acid ester. The problem of electrostatic adhesion of core particles has not been addressed; hence there is no need to select a matrix with a hydroxyl value of 60 or greater to prevent electrostatic adhesion of the core particles.

The Examiner disagrees.

As discussed *supra*, Akiyama et al. teaches polyglycerol fatty acids esters such as diesters comprised of triglycerols with fatty acids such as behenic acid forming ester linkages, i.e. the triglycerol behenic acid half ester of instant claim 29. It would be reasonable expected that the triglycerol behenic acid half ester of Akiyama et al. would possess the same hydroxyl value as instantly claimed. As discussed *supra*, Akiyama et al. clearly teach that the methods do not produce granules with a static charge. Accordingly, it would reasonably be expected that uncharged particles are preferred;

and it would have been within the purview of the skilled artisan to determine if the components and methods produced granules without a static charge. If charged particles were produced, it would have been within the purview of the skilled artisan to determine which matrix components would produce uncharged particles as required.

2) Claim 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akiyama et al. and British Plastics and Rubber (2001) as applied to claims 21-24, 28-30 and 33 above, and further in view of Kojima et al. (J. of Controlled Release, 2002).

Akiyama et al. and British Plastics and Rubber are discussed *supra*.

Akiyama et al. and British Plastics and Rubber do not teach a heart treatment before or after the coating step.

Kojima et al. teach methods of developing controlled release matrix pellets by annealing with micronized water-insoluble polymers (Abstract). Spray chilling by using a polyglycerol ester of a fatty acid is an alternative method of manufacturing matrix controlled release pellets (page 336, 1st column, 1st paragraph). Ethylcellulose was used as the water insoluble polymer and theophylline was used as the pharmaceutical (page 336, 2nd column, 2nd paragraph). The release rate of theophylline was decreased by annealing at 80°C for 4 h. Annealing of the matrix particle leads to alterations of the pellet structure and consequently, of the release properties (page 339, 1st column, 1st full paragraph). Sufficient annealing probably softens the polymer causing it to fill-in the interstices and resulting in the observed morphological changes. Thus the reduced porosity of annealed pellets result in decreased release rates and a prolongation of the

total release time (page 340, 2nd column, 1st paragraph). The theophylline release rate from annealed pellets can be controlled by varying the theophylline-to-polymer ratio and polymer properties (page 342, 2nd column, Conclusions).

Kojima et al. does not teach a matrix pellet core particles containing a pharmaceutically active substance and a matrix base material that has a hydroxyl value of 60 or greater and contains a polyglycerol fatty acid ester.

At the time of the invention, it would have been obvious to modify the method suggested by combining Akiyama et al. and British Plastics and Rubber to include the step of annealing at a temperature that softens the core, i.e. heat treatment, before or after coating since it is a method of providing the granules with controlled release properties. Since both the method of Kojima et al. and the method suggested by combining Akiyama et al. and British Plastics and Rubber are methods of preparing controlled release particles a combination of the methods would be expected to further control the release of active from the granules.

Since Kojima et al. teach that softening of the polymer in the core causes morphological changes that result in reduced porosity and decreased release rates and prolongation of release times, it would have been obvious to optimize the release of active by varying the annealing temperature, and thereby varying the degree of softening of the core. It would have been obvious to use the temperatures near the softening point or melting point of the polymer as a reference for the appropriate annealing temperature and it would have been within the purview of the skilled artisan to determine the softening point and/or melting point.

Applicant argues that Kojima et al. does not make up for the deficiencies of Akiyama et al. and Bartholomaeus et al.

The Examiner disagrees.

The 103 obviousness rejection over Akiyama et al. and Bartholomaeus et al. has been withdrawn. Accordingly, Kojima et al. is only required to provide motivation for combining with Akiyama et al. and British Plastics and Rubber.

Applicant alleges that the present invention achieves another remarkable effect, i.e. unexpected results, and points to Test Example 4, Figures 2 and 4 for support. The crystalline transition of the matrix material can be promoted by the heat treatment before fusion coating, whereby stable drug release control properties can be maintained even after long storage.

The Example and figures do not support the allegation of unexpected results since Applicants have not compared the invention to the closest prior art, i.e. Akiyama et al. which discloses substantially the same matrix component and pharmaceutical active. Therefore, it is not possible for the Examiner to determine if the results are unexpected. Further, Figures 2 and 4 are not clear insofar as the data is not identifiable. In Figure 2, the legend shows that the data generated for immediately after heat treatment and for after 2 months at 50°C are both represented by a solid circle; and in Figure 4, the legend shows that the data generated for after 2 weeks at 50°C and for after 2 months at 50°C are both represented by a solid square and the data

generated for after 2 weeks at 40°C and for after 2 months at 40°C are both represented by a solid triangle.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Darryl C. Sutton whose telephone number is (571)270-3286. The examiner can normally be reached on M-Th from 7:30AM to 5:00PM EST or on Fr from 7:30AM to 4:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached at (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Darryl C Sutton/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612